REMARKS

Claims 1-11 were presented for examination, and were variously rejected. Claims 2-4 have been canceled. Claims 1, 8 and 11 were amended. Claim 1 now requires n to be 1-3 instead of 0-3. This amendment deletes only one possibility from the definition of n (it excludes n = 0), thus it adds no new matter. Claims 8 and 11 are amended to recite the structural limitations of original claim 1, in view of the amendment to claim 1. Accordingly, the amendments add no new matter. Entry of these amendments is respectfully requested.

The grounds for rejection have been carefully considered. The applicant now respectfully requests reconsideration of the claims in view of the following comments.

Rejections Based on 35 U.S.C. § 112

Enablement

Claims 8-10 were rejected as allegedly indefinite because "claims 8-10 fail to particularly point out variation of operable conditions and recipient compounds for amination to proceed." According to the Examiner, "the scope that is enabled is limited to the 'Amination of methyl indole-3-carboxylate' (Specification Example 3)." The applicant traverses this rejection.

It is almost never proper to limit claims to the specific examples provided in the specification. The application only needs to provide enablement commensurate in scope with the claims, not an exhaustive recitation of all possible variations. According to MPEP 2164.08:

> All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Moreover, "As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *AK Steel Corp. v.*

Sollac, 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003); *In re Moore*, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971)."

The specification teaches that the reagents disclosed are useful to aminate the nitrogen of various recipient compounds. Specific examples and additional guidance provided would enable one of ordinary skill to adjust reaction conditions to N-aminate various substrates without undue experimentation: guidance is provided in the selection of suitable solvents (paragraph [0010] specifies a "polar aprotic solvent", and Example 3 demonstrates that DMF is suitable), and selection of a suitable reaction temperature is a routine matter, well within the ordinary skill in the art. A declaration from one of the inventors is provided herewith as **Exhibit A**, stating that one of ordinary skill would know to refer to analogous methods in the literature to identify appropriate conditions for using the improved aminating agents of the claim (Decln. Item 9), and that analogous reactions were known prior to the filing date of the application. A list of selected references describing analogous reactions is provided as **Exhibit C**.

The specification further teaches that aminating reagents that accomplish the same transformation are well known in the art, but suffer from safety concerns: they tend to explode. (Para. [0003].) Accordingly, there is relevant knowledge in the art about the use of aminating reagents that perform the same transformation as those claimed herein, and correspondingly less guidance on the details of such uses are needed: the application need not include, and preferably omits, what is well known. The optimization of the reaction conditions to use the claimed aminating reagent would be a routine matter once the reagent and its uses are disclosed; the attached Declaration is evidence of that (see para. 9). Accordingly, the rejection based on alleged lack of enablement can be withdrawn.

Written Description

Claims 8-10 were also rejected for alleged failure to comply with the written description requirement. According to the Examiner, 'a recipient compound' is not clear, and the application lacks description of temperature conditions that are needed.

The applicant traverses this rejection. The terms in a claim must be read in light of the specification. The specification refers to literature in which aminating agents are known to transfer NH_2 from an oxygen of a donor compound (aminating agent) to a nitrogen of a recipient compound have; those aminating agents have hazardous properties that are solved by the present invention. However, the prior art provides ample information on the types of compounds that can be aminated by such aminating agents; accordingly, one of ordinary skill would have understood the term 'recipient compound' in this context to refer to compounds that undergo amination reactions with such aminating agents. The declaration supports this assertion. (Decln. Para. 4-6.) Such compounds were well known in the art when the application was filed: by way of examples, **Exhibit C** provides a number of abstracts for references that describe aminations of nitrogen atoms of various recipient compounds by transfer of NH_2 from an oxygen of a donor compound (aminating agent). All of the references show publication dates that precede the filing date of the application, and were thus part of the knowledge generally available in the art at that time.

Furthermore, the specification indicates that the recipient compound can be an indole; accordingly, claim 10, which requires the recipient compound to comprise indole, would have been understood to indicate that the indole of the recipient compound was to be aminated, as it is in the examples.

According to the Examiner, "The claims embraced recipient compounds and conditions of US 6,248,925 and US 5,589,596..." The applicant sees no possible relevance of those references to the claimed reactions or reaction conditions: no reactions in the cited references appear to relate to an N-amination reaction or to the use of a reactant of formula (1). One of ordinary skill would not have understood 'recipient compound' to extend to all known compounds, only those reasonably capable of being aminated by the aminating agents of the claim, as demonstrated by analogous reactions known in the art.

The Examiner asserts that "recipient compounds and conditions under which amination can proceed and their description are particularly pertinent at the point of novelty over the art." Respectfully, the nature of the recipient compound, or the specific conditions for the amination

reaction, are not the point of novelty; the novelty resides in the nature of the aminating reagent, which is highly effective yet less unstable than those of the prior art. No references were cited where claims 8-10 relied on the recipient compound for novelty. The temperature for the amination reactions is also not a point of novelty: optimization of temperature for a reaction is a routine task; and there is ample disclosure in the art to provide additional guidance based on prior art aminating agents and their uses. Accordingly, the rejection based on written description can be withdrawn.

Rejections Based on 35 U.S.C. § 102

Claims 2-4 were rejected over two cited references. Those claims have been canceled, rendering this rejection moot. Therefore, this rejection can be withdrawn.

Rejections Based on 35 U.S.C. § 103

Claims 1-7 were rejected as obvious in view of Van Assche (US 4,472,194) or Tessier (US 4,801,717). According to the Examiner, "the difference between the species claim 7 and the anticipated compounds (US 4,472,194, column 1, lines 46-47) is that instead of the base structure having only one trifluoromethyl substituent, the instant claimed species differ from the prior art compounds by one additional trifluoromethyl substituent in the ortho position of the base compound. US 4,801,717 discloses the base compound substituted 'with at least one' trifluoromethyl substituent (US 4,801,717 columns 1 and 2) occupying any position of the ring." The Examiner then says, "One of ordinary skill in the art would be in possession of such modification with one trifluoromethyl aryl substitution because both prior art references are of analogous art and thus such modification has been clearly guided to one skilled in the art." Finally, the Examiner concludes, "One having ordinary skill in the art would be motivated to make such modification knowing that reasonable success has been demonstrated in analogous compounds (US 4,801,717, columns 4 and 5). It is prima facie obvious to modify one known compound with *attributes* proven in analogous compounds."

The applicant traverses this rejection to the extent that it could be applied to the claims as currently amended.

First, this rejection appears to be directed at claim 7 only. The Examiner discusses this only as it relates to adding a trifluoromethyl group to a specific embodiment that the Examiner refers to as the "base" compound. However, the rejections must be applied to the claims individually, and the Examiner must consider 'the invention as a whole' and the prior art teachings as a whole. MPEP 2141.02. An obviousness analysis directed at a single species claimed in claim 7 does not provide a basis for an obviousness rejection of other claims.

Second, The Examiner appears to rely on a combination of the references to reject the claims, saying that "US 4,801,717 discloses the same optional substituents for the common compound (see columns 1 and 2) as disclosed in US 4,472,194 (see column 1)", and noting that the compounds are used for a common purpose. However, US 4,472,194 does not disclose any "optional substituents": it discloses a small number of specific compounds, which are all substituted phenoxyamines. That group of compounds does not overlap with the subject matter of claim 1 as amended, or of claim 7 as originally presented. It is unclear how its disclosure is relevant to the asserted obviousness rejection.

The Examiner says that the '717 patent (Tessier) "discloses the same optional substituents for the common compound...as disclosed in US 4,472,194." But that is not accurate: the '717 patent discloses a very, very broad list of substituents (the '194 patent discloses far fewer) on a wide array of aryl groups, creating a vast genus, and the best guidance toward specific compounds that Tessier provides is perhaps the claims, which require the aromatic group to be a quinoline (a bicyclic group) rather than a phenyl as would be required for the instant claims. Furthermore, Tessier excludes by proviso a list of compounds that appears to correspond to those in the '194 patent. (Tessier, col. 2, lines 18-24.) Thus it is unclear why one would look to Tessier to modify the compounds of the '194 patent, or vice versa: their compound genuses are expressly different, with no overlap; and the preferred compounds in Tessier have bicyclic aryl groups rather than phenyls.

Third, the disclosure of a broad genus does not render obvious all species within it. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed

compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."). See, e.g., *In re Brouwer*, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996) ("[T]he mere possibility that one of the esters or the active methylene group-containing compounds . . . could be modified or replaced such that its use would lead to the specific sulfoalkylated resin recited in claim 8 does not make the process recited in claim 8 obvious `unless the prior art suggested the desirability of [such a] modification' or replacement.") (quoting *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984); *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991) ("[A] proper analysis under Section 103 requires, inter alia, consideration of . . . whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process."). The size of the prior art genus is highly relevant in an obviousness analysis; the genus in Tessier is quite large. The Examiner has not provided reasoning to show why one of ordinary skill would have selected a compound similar to formula (1) for modification, from among the *many* possible starting points present in Tessier; or why one would have made the particular modifications required to form a compound within the present claims. The reference does not appear to provide any specific guidance toward such compounds, *e.g.*, it does not disclose or suggest any specific compound having a Nitro group and a trifluoromethyl group plus an additional substituent, let alone what additional substituent to add, or where to put it. It does not, for example, disclose or suggest a compound having two trifluoromethyl groups as required by claim 7.

The Examiner says Tessier teaches a base compound "with at least one" trifluoromethyl substituent. But that is very misleading: Tessier teaches an aryloxyamine Ar—ONH_2 where the aryl group is very broadly defined, and where the aryl group is "optionally substituted with at least one member" selected from a large group of very diverse substituents. The exemplified compounds and the stated preferences in the refernece both suggest that the compounds are preferably substituted with halogen and nitro groups, e.g. at column 3, Tessier says the preferred compounds are ones "wherein Ar is phenyl substituted with at least one of the above substituents, especially when at least one is nitro and especially when one is a p-chlorine, and their non-toxic pharmaceutically acceptable acid addition salts." (Tessier, col. 3, lines 15-19.) It does not clearly

guide the reader toward the required trifluoromethyl substitutent in formula (1), or toward a phenoxyamine having three substituents as required by claim 1. Indeed, the *claim* in Tessier relates to a quinoline rather than a phenyl compound. Claim 1 as amended requires both a trifluoromethyl and a phenoxyamine, and includes further limitations as well. Accordingly, the reference does not provide guidance to allow one to identify the genus of compounds claimed in claim 1.

Finally, the Examiner concludes with this confusing statement: "It is prima facie obvious to modify one known compound with *attributes* proven in analogous compounds." Neither the meaning nor the origin of this assertion is clear, but it conflicts with established precedent. The courts and the MPEP clearly say that there are no *per se* rules of obviousness. (MPEP 2144.08: "Use of per se rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. 103. See, e.g., *In re Brouwer*, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996); *In re Ochiai*, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995); *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994).")

Obviousness is a fact-based determination in each case, and the Office must provide reasoning to show why one of ordinary skill would have arrived at the *claimed invention* based on the particular facts at issue. According to MPEP 2144.08 (II), "In light of the findings made relating to the three Graham factors, Office personnel should determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed prior art genus. See, e.g., Ochiai, 71 F.3d at 1569-70, 37 USPQ2d at 1131; Deuel, 51 F.3d at 1557, 34 USPQ2d at 1214.

In claim 1, the claimed invention is a small genus of compounds; even if that genus were encompassed by the very broad genus in Tessier (US 4,801,717), it is not rendered obvious for that reason alone, nor is a subgenus (or the invention as a whole) rendered obvious merely because a single compound within the subgenus might be considered obvious. *In re Baird.*

The invention as a whole must be considered in order to establish an obviousness rejection. No motivation to select the genus of claim 1, or the sub-genus or the species of claims 5-

7, was identified by the Examiner. There is no *per se* rule of obviousness, and the Examiner did not identify motivation from the reference to select a compound of formula (1) as a starting point; or motivation to modify that compound in a way that would meet the additional limitations of claim 1, which now requires adding 1-3 additional substituents to the compound. Nor has the Examiner shown that one would have been motivated to select the particular substituents required by claim 1 from among the broad array of substituents disclosed in the Tessier reference. Accordingly, no *prima facie* case of obviousness has been established for claim 1, and this rejection can be withdrawn.

Similarly, no *prima facie* case of obviousness for claims 5-7 was established, especially in light of the amendment to claim 1, from which these claims depend. The Examiner did not identify motivation from the reference to select a compound of formula (1) for modification; or motivation to modify such a compound to meet the additional limitations of claims 5-7, which now require adding exactly one substituent 'R' to the compound (claim 5); and require the substituent to be placed in a specific position (claim 6); and require the added substituent to be CF_3 (claim 7). Accordingly, no *prima facie* case of obviousness has been established for claims 5-7, and this rejection can be withdrawn.

Claim 11 was also rejected over the '194 patent and/or Tessier. Claim 11 describes a method to make a compound of formula (1) from a compound of formula (2), using a protected form of hydroxylamine that is either a hydroxylacylamidate or Boc-hydroxylamine. According to the Examiner, "the instant claim [sic] method differs from the prior art method by using an N-protected hydroxylamine to obtain the compound of claim 1. US 4,801,717 (Example 1) generically discloses the process of making claim 1 compounds, beginning with a fluoro precursor to obtain a hydroxylamine. ... One having ordinary skill in the art would be in possession of such modification of utilizing an N-protected hydroxylamine in the synthesis of the hydroxylamine compounds of claim 1 because the inclusion of an N-protective step in an operable analogous synthetic process is conventional and routine to the chemical art because N-protecting enhances specificity of functional sites....One having ordinary skill in the art would be motivated to make such modification knowing

that reasonable success has been demonstrated in analogous methods. It is prima facie obvious to modify one known method with attributes proven in analogous methods."

The applicant traverses this rejection. As discussed above, the obviousness determination must be made based on the facts of the situation at hand: there are no *per se* rules of obviousness. *In re Brouwer*.

First, the applicant must point out that Tessier (US 4,801,717) discloses a method to make its compounds using either hydroxylamine or a protected hydroxylamine. At column 5, it depicts HO—$N(R)_2$, where the R's can be H or they can, taken together with N, form a phthalimido group. (Tessier, col. 5, lines 40-46). Thus the hydroxylamine can be introduced as N-hydroxyphthalimide; then, after the N-hydroxy compound is attached to the aryl ring, the phthalimide can be removed with hydrazine. (Tessier at col. 5, lines 55-56). However, Tessier does not disclose other protected hydroxylamines or reasons to use them; it certainly does not provide a reason to choose the particular protecting groups recited in claim 11.

The Examiner says the claimed method would have been obvious "because the inclusion of an N-protective step in an operable analogous synthetic process is conventional and routine to the chemical art because N-protecting enhances specificity of functional sites." It is not enough to establish a *prima facie* obviousness rejection, however, for the means to modify the teachings of a reference to be possible, known or 'conventional'. (See MPEP 2143.01, "A statement that modifications of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).")

For a claim to be rejected as obvious, there must be some teaching or motivation in the art to make the modifications required to arrive at the claimed invention. The Examiner asserts that

"N-protecting enhances specificity of functional sites." That is a very broad generalization for which no support or explanation was provided. Even if true, though, it does not render obvious the claimed invention, which applies a specific choice of protecting groups to a specific reactant to effect a specific transformation. The obviousness analysis is a fact-based one, not one of *per se* rules. (MPEP 2144.08: "Use of per se rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. 103. See, e.g., *In re Brouwer*, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996); In re Ochiai, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995); *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994).") The decision to modify a synthesis method by using a protection / deprotection step can be an invention, and selection of a particular protecting group for a specific application can be an invention. The Examiner has offered no reason why one of ordinary skill would have chosen to employ a protecting group in the particular transformation of claim 11, when it was known to work without one; or why one would have selected the specific protective groups specified in claim 11. In fact, the Examiner has not demonstrated that the alkyl hydroxylacylamidate would have been recognized as a 'protecting group.'

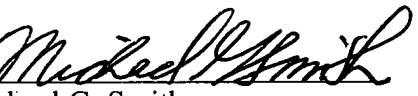
Also, the conventional knowledge that protective groups can enhance selectivity is only relevant if the reference discloses a need for "enhanced selectivity." Tessier teaches that hydroxylamine works without protection; indeed it says, "In a preferred mode of the process the Hal of the compound of formula II is fluorine or bromine **and the Rs of formula III [formula III is the $HON(R)_2$ species] are hydrogen**..." (Tessier at col. 5, lines 58-60.) The *reference itself* says that the non-protected version of the hydroxylamine reactant is preferred over the only protected form it discloses. Therefore, the reference does not provide motivation to experiment with other protecting groups: instead, it teaches away from their use. Thus the reference does not provide motivation to make the modifications needed to arrive at the claimed invention; and it cannot provide motivation to select the particular protecting groups of claim 11, which are not disclosed or suggested by the cited references. Accordingly, this obviousness rejection can be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 219002030100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: May 8, 2006

Respectfully submitted,

By 

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